

## NIEHS-NCI collaboration leads to novel analysis of anticancer therapeutics

By Monica Frazier

Scientists at NIEHS collaborated with National Cancer Institute (NCI) researchers to assess the therapeutic results of combination anticancer treatments. Their findings, published online Jan. 12 in the journal Frontiers in Genetics, demonstrated the potential for their toxicogenomics approach to predict toxicity risks of cancer therapies that use a combination of drugs.

## Synergistic expertise across NIH campuses

Pierre Bushel, Ph.D., staff scientist in the Biostatistics and Computational Biology Branch, led the NIEHS team. His group developed the novel Extracting Patterns and Identifying co-Expressed Genes (EPIG) methodology, one of several bioinformatics tools developed at NIEHS.

Myrtle Davis, Ph.D., chief of the Toxicology and Pharmacology Branch

(http://dtp.nci.nih.gov/branches/tpb/default.htm)

at NCI, noted that she first came to know of Bushel's work through a 2010 article in the National Institute of Health (NIH) newsletter The NIH Catalyst.

(http://www.nih.gov/catalyst/2010/10.12.01/catalyst\_v18i6.pdf)

The analytical approach Bushel's group used matched perfectly with what her group sought for in their studies on combination anticancer agents. "The research effort of NIEHS in bioinformatics and our NCI program focus on effects of anticancer therapy were highly synergistic," Davis said.

## The sequence of chemotherapeutics matters

Treating cancer typically requires a combination of drugs. Combination treatments often have more severe toxicity and undesirable side effects, leading clinicians to reduce dosages. Bushel and Davis sought to use a systems-based computational approach to perform a nonclinical assessment of combination treatments. As proof of principle, they studied two well-known and commonly used chemotherapy drugs, topotecan and oxaliplatin.

Bushel and Davis hypothesized that they could use early responses of messenger RNA in tissues, after a single dose of one drug alone and after dosing with the second drug, to infer enhanced toxicity. Their hypothesis proved correct. The researchers found that a single dose of topotecan resulted in bone marrow lesions after 1 hour. Oxaliplatin alone did not result in such lesions until 6 hours after treatment. When a combination therapy was used, lesions were more severe when topotecan was administered first.

Using EPIG analysis, the scientists identified the prominent pathways within bone marrow affected after treatment with the two drugs. These included genes that alter bone marrow histone biology, chromatin remodeling, DNA repair, bone regeneration, and respiratory and oxidative phosphorylation. In particular, the up-regulation of DNA repair and chromatin remodeling pathways are in line with the known mechanism of topotecan's toxicity as an inhibitor of the enzyme topoisomerase I.

The pair of investigators intend to extend this work. "The success of the collaboration on the bone marrow data set will certainly carry over to investigate the oxaliplatin-topotecan combination effect on gene expression in other rat tissues," said Bushel. "In the long run, we are hoping to reveal a few mechanistic signatures that may be applied *in vivo* or *in vitro*," Davis added.

Citation: Davis M, Li J, Knight E, Daniels KK, and Bushel PR.

(http://journal.frontiersin.org/Journal/10.3389/fgene.2015.00014/abstract)

2015. Toxicogenomics profiling of bone marrow from rats treated with topotecan in combination with oxaliplatin: a mechanistic strategy to inform combination toxicity. Front Genet [online 12 Jan 2015; doi

10.3389/fgene.2015.00014].



Bushel noted that other NIH staff played a role in the collaboration, including Elaine Knight, Ph.D. and Sandy Eldridge, Ph.D., from NCI, and Jianying Li at NIEHS. (Photo courtesy of Steve McCaw)



"A nonclinical option can supplement the current therapeutic strategy by providing means to determine when combination toxicity presents a high risk," said Davis. "Or it might help identify risks to organs from combination therapy, which wouldn't be expected from the single drug profiles, so that clinicians could closely monitor them." (Photo courtesy of Myrtle Davis)

(Monica Frazier, Ph.D., is an Intramural Research Training Award fellow in the NIEHS Mechanisms of Mutation Group.)

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